Track 2: Case Study Efficacy Biomarker Validation

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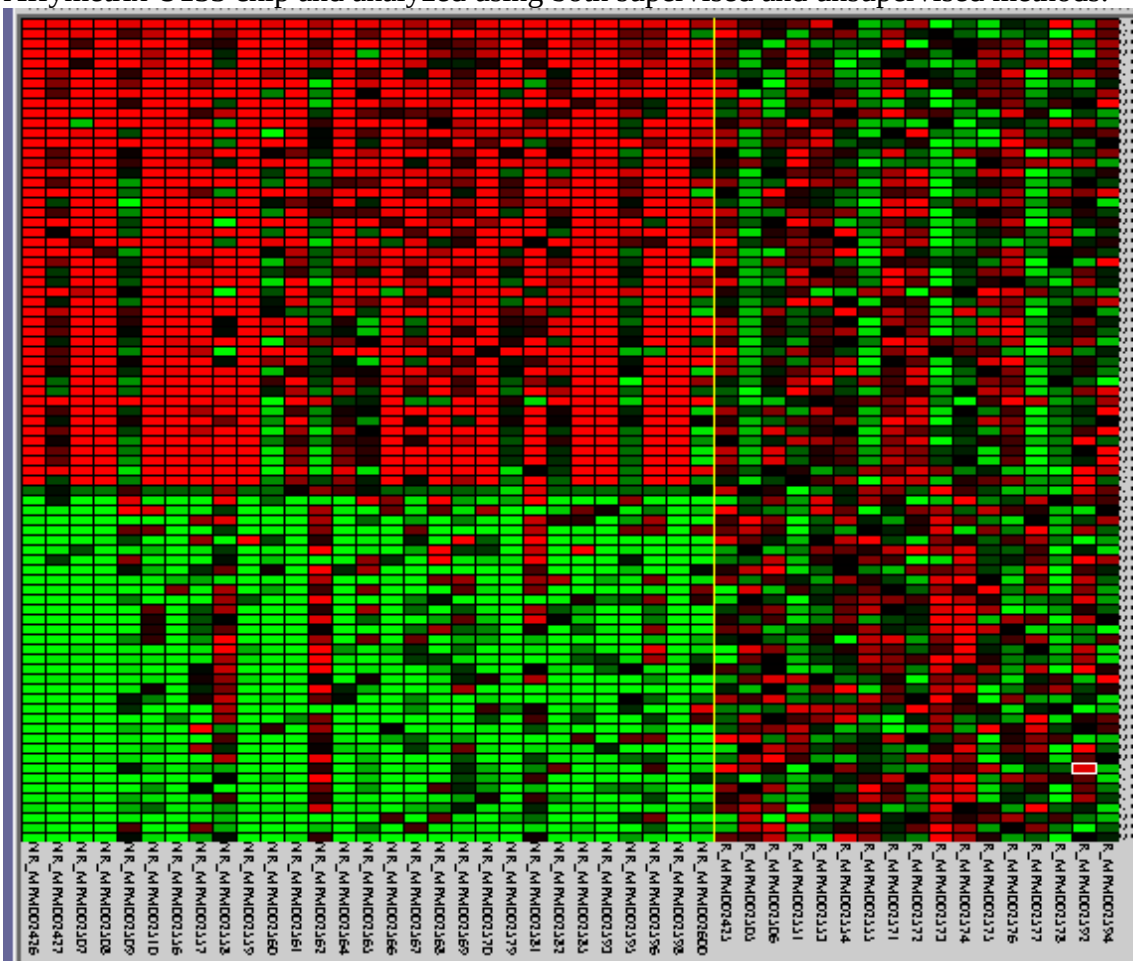
Background

A sponsor has conducted a pharmacogenomic substudy as part of the development program for a novel anti-neoplastic agent. Tumor tissue samples were collected at the baseline time in a multicenter phase 2 clinical trial of the new agent vs. standard therapy. Samples were collected from 70% of participants, but only about 1/3 of the total population yielded evaluable samples. Gene expression profiles were measured using the Affymetrix U133 chip and analyzed using both supervised and unsupervised methods.



The evaluable patients were divided into a training set and a validation set, and signatures of 5-30 genes were found to be significantly associated with survival and with response to the investigational drug but not the control treatment. The best performing 8-gene set had a sensitivity of 80% and specificity of 84% in distinguishing responder vs. non-responders to the novel agent. The response rate in the marker negative patients was

12%; in the marker-positive patients it was 56%. The prevalence of the marker-positive patients was 40% of the (evaluable) patients.

The sponsor has submitted these data under the VGDS mechanism, and is planning to begin a phase 3 trial as soon as possible.

Questions

1. Should the phase 3 study be done only in marker-set positive patients?

2. If the sponsor proceeds with such a trial, the sample size could be 1/3 that of an all-comers study to achieve the same number of outcomes. However, safety data will still be needed in marker-negative patients. How should the sponsor proceed?

3. Will a diagnostic test be needed based on these results?

4. How can the current method be adapted to clinical use?

5. What type of qualification and validation will be needed?

6. Will approval be required for a paired diagnostic-therapeutic product?

7. What additional studies will need to be done? Can this be completed in time to impact the proposed phase 3 study? If not, how much delay is a reasonable trade-off?

Fig. 1 Proposed Baseline Process Map for Validation of Clinical Biomarkers